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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

KOLKER, DANIEL E

ART UNIT

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PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/517,653	Applicant(s) WEST ET AL.	
	Examiner DANIEL KOLKER	Art Unit 1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 November 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-17 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

1. The remarks and amendments filed 25 November 2008 have been entered. Claims 1 and 3 - 17 are pending and under examination.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 November 2008 has been entered.

Withdrawn Rejections and Objections

3. The following rejections and objections set forth in the previous office action are withdrawn:

A. The rejection under 35 USC 112, first paragraph is withdrawn in light of the amendments; applicant is no longer claiming a method of "neuronal regenerative growth", which the examiner had considered to be not enabled over its full scope.

Maintained Rejections

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 and 4 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Penkowa (2002. *Journal of Comparative Neurology* 444(2):174-189), as evidenced by Sigma M9542 and Garrett (2000. *The Prostate* 43:125-135).

This rejection stands for the reasons previously made of record and explained in detail below. Claim 1 as amended is drawn to "[a] method of stimulating axonal outgrowth comprising directly contacting a target living neuron or live neuronal area to a solution of the metallothionein isoform MT-IIA." As set forth previously, Penkowa teaches administering metallothionein 2 (also called MT-2 in the reference) to mice. At p. 176 first paragraph the reference teaches administering the compound to normal mice, some of which had been treated with the compound 6-AN which damages the brain (see p. 175 second column). The examiner has set forth a prima facie case that the MT-II administered by Penkowa either is, or is an obvious variant of, MT-IIA as recited in the claim. This has not been refuted by applicant.

Penkowa teaches administration of MT-II by the intraperitoneal route (p. 184 end of first column). While MT-II normally does not cross the blood brain barrier (BBB), Penkowa provides evidence that the MT-II administered after 6-AN treatment in fact does reach the brain. Penkowa states that "we have observed that i.p.-injected Zn-MT-2 is readily observed in the extracellular space of the areas of CNS with infiltrations, 30 - 60 minutes after Zn-MT-2 injection. In contrast, in animals with no clinical symptoms; therefore with a normal BBB, no extracellular MT was detected". The reference also teaches that "[i]n the present study, it is likely that the injected Zn-MT-2 entered the CNS in the 6-AN-treated mice because it is well known that the BBB is dramatically affected by this gliotoxin" (all quoted text from p. 186 first paragraph). Since Penkowa administered an agent that disrupts the BBB, the MT-2 was able to come into direct contact with the relevant neurons, even after peripheral administration. Thus,

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the Penkowa reference teaches every element of claim 1. The examiner notes that claim 1, which recites "directly contacting" does not recite any particular route of administration. Rather the claim requires that contact between the drug (MT-IIA) and the neurons be direct.

Claim 4 is rejected as it recites a product-by-process limitation ("wherein said MT-IIA is produced by chemical synthesis or by production in genetically manipulated cells or organisms") which does not distinguish the claimed invention over the prior art. There is no evidence of record that the product made by the processes recited in claim 4 are any different than those made by other means.

5. Claims 1, 4, and 17 stand rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Giralt (2002. *Experimental Neurology* 173:114-128, available online 25 February 2002).

This rejection is maintained for the reasons previously made of record and explained in more detail herein. Briefly, Giralt teaches administration Zn-MT-2 to mice that had received a head injury, recited in claim 17. As set forth in the previous office actions, MT-2 administered by Giralt is either the same as, or an obvious variant of, MT-IIA as recited in the claims.

Giralt provides evidence that the cryolesions performed disrupt the BBB, thereby allowing direct contact between the MT-2 administered and the relevant target neurons; see p. 120 paragraph spanning the two columns. Since Giralt performed interventions, specifically cryolesions, that disrupt the BBB, the MT-2 was able to come into direct contact with the relevant neurons, even after peripheral (i.p.) administration. Thus, the Giralt reference teaches every element of claim 1. The examiner notes that claim 1, which recites "directly contacting" does not recite any particular route of administration. Rather the claim requires that contact between the drug (MT-IIA) and the neurons be direct.

Claim 4 is rejected as it recites a product-by-process limitation ("wherein said MT-IIA is produced by chemical synthesis or by production in genetically manipulated cells or organisms") which does not distinguish the claimed invention over the prior art. There is no evidence of record that the product made by the processes recited in claim 4 are any different than those made by other means. Claim 17 is rejected as the animals had a head injury.

Claims 1, 4, and 6 - 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penkowa (2002. *Journal of Comparative Neurology* 444(2):174-189).

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The reasons why claims 1 and 4 stand rejected as anticipated by or obvious over Penkowa are set forth above. While the reference teaches administering a total of 17.5 ug Zn-MT-2 in saline per day, divided into three separate doses (p. 176 first paragraph), Penkowa does not explicitly teach that the solution has a concentration of “up to about 5 ug/ml” as recited in claim 6 or “about 5 ug/ml” as recited in claim 7. Additionally, Penkowa teaches that endogenous MT-1, transcribed off a transgene, is sufficient to reduce CNS degeneration but does not explicitly teach administering this protein as encompassed by claims 8 – 11, as the protein is endogenous to the transgenic mice.

It would have been obvious to one of ordinary skill in the art to adjust the concentration of MT-2 administered by Penkowa. Changing the concentration of a composition is not supportive of patentability (MPEP § 2144.05(II)(A)). As Penkowa teaches a method according to claims 6 – 7 that differs only in that the prior art does not disclose the actual concentration of the composition, and altering the concentration of the active ingredient would have been obvious to one of ordinary skill in the art, claims 6 – 7 are unpatentable over Penkowa. The motivation to alter the concentration of the active ingredient would be to find a volume of injection suitable for the patient.

It also would have been obvious to one of ordinary skill in the art to coadminister MT-1 recited in claims 8 - 9 along with MT-2, with a reasonable expectation of success. The motivation to do so would be to provide additional neuronal protection. It would be reasonable to expect success as Penkowa teaches that endogenous MT-1 also has positive effects on neural health. The reasons why claims 10 – 12 are included in this rejection are set forth in the previous office action.

This rejection stands for the reasons previously made of record. Applicant did not separately traverse the examiner's determinations that the limitations recited in claims 6 - 12 would have been obvious to one of ordinary skill in the art, but rather argued that Penkowa does not anticipate claim 1. As set forth in the rejection under 35 USC 102/35 USC 103 above, the rejection of claims 1 and 4 stands.

6. Claims 1 – 12 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Penkowa (2002. Journal of Comparative Neurology 444(2):174-189) in view of FR 2813529, cited on IDS filed 13 December 2004.

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The reasons why claims 1, 4, and 6 – 12 are anticipated by or obvious over Penkowa are set forth above. Briefly Penkowa teaches administration of MT-IIA is protective of neurons, and teaches compositions comprising MT-IIA. Penkowa suggests that metallothioneins can be used in treating CNS diseases (p. 187 end of first column). However Penkowa used rabbit metallothionein, and does not teach administration of human MT-IIA as recited in claims 3 and 5.

FR 2813529 teaches compositions comprising human MT-IIA, which are on point to claims 3 and 5. However '529 publication does not teach administering the compositions such that target neurons or neuronal areas are exposed to the MT-IIA-containing compositions.

It would have been obvious to one of ordinary skill in the art to modify the methods of Penkowa to use the human MT-IIA taught in '529 publication, with a reasonable expectation of success. The motivation to do so would be to ensure less of an immune response when treating human patients. The artisan would be motivated to make this substitution, thereby arriving at the invention of claims 3 and 5, because the human MT-IIA sequence was known in the art and shown by '529 publication to be suitable for administration to humans, and because the artisan of ordinary skill would immediately understand that using a protein from a foreign species would increase the likelihood of an adverse immune reaction.

Applicant did not separately traverse the examiner's determinations that the limitations recited in claims 3 and 5 would have been obvious to one of ordinary skill in the art given the teachings of the '529 publication, but rather argued that Penkowa does not anticipate claim 1. Since claims 1 and 4 stand rejected as set forth above, this rejection stands as well.

New Rejections

Claim Rejections - 35 USC § 103

7. Claims 1, 4, and 6 - 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penkowa (2002. Journal of Comparative Neurology 444(2):174-189) in view of Deguchi 2000 (Pharmaceutical Research 17(1):63-69) and Yoshimura 2001 (Proc Natl Acad Sci USA 98(10):5874-5879).

The reasons why claims 1, 4, and 6 - 12 are anticipated by, or obvious over Penkowa are set forth above. Briefly Penkowa teaches that MT-2, which is patentably indistinct from MT-IIA recited in the claims, decreases 6-AN-induced degeneration of gray matter when administered peripherally. Penkowa also teaches that in normal animals, MT-2 does not cross

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the BBB, but that the reason why the drug reaches neural cells in this particular case is because of the BBB-disrupting effects of 6-AN (p. 186 first column). However, Penkowa does not teach direct injection of the drug to a neuron or a neuronal area as recited in claim 13.

Deguchi teaches that basic fibroblast growth protein (also called bFGF) is generally excluded from the blood brain barrier. Deguchi presents results of a series of experiments to determine how much bFGF enters the brain after being administered in the blood. At p. 69 final paragraph Deguchi indicates that less than 1% of the injected dose reaches the brain, and concludes that in order for it to have therapeutic efficacy within the brain more of it will need to be delivered. One solution proposed by Deguchi is to attach the bFGF to a BBB-transport molecule. However Deguchi does not teach administration of metallothionein.

Yoshimura teaches administration of bFGF by injection of a nucleic acid that encodes the protein into the brain. See for example p. 5875, first column, last two paragraphs. The reference provides evidence that this method is sufficient to get the bFGF protein into the brain; see for example Figure 4. However Yoshimura does not teach administration of metallothionein.

It would have been obvious to one of ordinary skill in the art to modify the methods of Penkowa by directly administering the MT-2 within the brain, thereby arriving at the invention of claim 13. The motivation to do so comes from the prior art references themselves. Penkowa teaches that when the BBB is not disrupted, MT-2 does not cross this barrier. An artisan of ordinary skill would understand that this means the protein cannot have its therapeutic effect. The references by Deguchi and Yoshimura, taken together, show that one solution to the problem of getting proteins excluded by the BBB into the brain is to inject them directly into the brain, thereby guiding the artisan of ordinary skill to perform the steps recited in claim 13.

8. Claims 1, 4, 6 - 13, and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penkowa in view of Deguchi and Yoshimura as applied to claims 1, 4, and 6 - 13 above, and further in view of Asanuma (2002. Neuroscience Letters 327:61-65; available online 21 April 2002).

The reasons why claims 1, 4, and 6 - 13 are anticipated by or obvious over Penkowa are set forth above. Briefly Penkowa teaches administration of MT-IIA is protective of neurons, and teaches compositions comprising MT-II, which is either the same as or an obvious variant of MT-IIA. Penkowa suggests that metallothioneins can be used in treating CNS diseases (p.

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187 end of first column). While Penkowa does not teach administration within the brain in those patients without a disrupted blood brain barrier, Deguchi and Yoshimura indicate that this is an effective way to get a drug that does not cross the barrier into the brain. However none of these references explicitly teaches a method of treating Parkinson's disease by administering metallothioneins as encompassed by claim 15.

Asanuma teaches that mice which lack both MT-I and MT-II are exceptionally susceptible to the toxic effects of 6-OH dopamine. See for example Figure 1, top panels. 6-OHDA is a chemical used to kill dopaminergic neurons, and administration of 6-OHDA is an art accepted animal model of Parkinson's disease. Asanuma teaches that the results indicate that both MT-I and MT-II have neuroprotective effects for Parkinson's (see p. 63 final paragraph), and suggest that the protective effects of these proteins are consistent with their known free-radical-scavenging roles. However Asanuma does not explicitly teach administering MT-IIA for treatment of Parkinson's disease as recited in claim 15.

It would have been obvious to one of ordinary skill in the art to administer MT-IIA, as taught by Penkowa, for treatment of Parkinson's disease, as suggested by Asanuma. The motivation to do so would be to effectively treat the disease. It would be reasonable for the artisan of ordinary skill to expect success, as Asanuma teaches that the lack of MT-I and MT-II leads to increased likelihood of death of dopaminergic neurons, the cause of Parkinson's disease, in the presence of certain toxins. Additionally Asanuma teaches the free-radical scavenging properties of these proteins, and teaches how these properties would be helpful in treatment of Parkinson's. Deguchi and Yoshimura indicate that if a drug does not cross the BBB (as is the case with MT-2 in normal patients; see Penkowa), administering it within the brain can ensure that the drug reaches its target neurons.

9. Claims 1, 4, 6 - 14, and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Penkowa in view of Deguchi and Yoshimura as applied to claims 1, 4, and 6 - 13 above, and further in view of Walsh (US Patent Application Publication 2002/0155170, published 24 October 2002, filed 30 November 2001, claiming benefit of a provisional application filed 30 November 2000).

The reasons why claims 1, 4, and 6 - 13 are anticipated by or obvious over Penkowa are set forth above. Briefly Penkowa teaches administration of MT-IIA is protective of neurons, and teaches compositions comprising MT-II, which is either the same as or an obvious variant

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of MT-IIA. Penkowa suggests that metallothioneins can be used in treating CNS diseases (p. 187 end of first column). While Penkowa does not teach administration within the brain in those patients without a disrupted blood brain barrier, Deguchi and Yoshimura indicate that this is an effective way to get a drug that does not cross the barrier into the brain. However none of these references explicitly teaches a method of treating Alzheimer's disease by administering metallothioneins as encompassed by claim 14 or treatment of motor neuron disease as recited in claim 16.

Walsh teaches that Alzheimer's disease (AD) is likely caused by a metallothionein disorder; see paragraphs [0118] – [0119]. Specifically, Walsh teaches that the plaques associated with AD result from free Cu and Zn ions, and that these plaques as well as the symptoms of AD will be ameliorated by metallothioneins. Walsh also teaches that familial amyotrophic lateral sclerosis symptoms worsen when metallothionein levels decrease (paragraph [0120]); this is a specific type of motor neuron disease. Walsh teaches and claims administration of a pharmaceutical composition which increases the amount of metallothioneins for treatment of Alzheimer's disease and the motor neuron disease familial amyotrophic lateral sclerosis, which is on point to instant claims 14 and 16 (see Walsh paragraph [0120] and claims 42 – 43). However Walsh does not teach administering MT-IIA for treatment of Alzheimer's disease as recited in claim 14 or for treatment of motor neuron disease.

It would have been obvious to one of ordinary skill in the art to administer MT-IIA, as taught by Penkowa, for treatment of Alzheimer's disease and the motor neuron disease, as suggested by Walsh. The motivation to do so would be to effectively treat the diseases. Deguchi and Yoshimura indicate that if a drug does not cross the BBB (as is the case with MT-2 in normal patients; see Penkowa), administering it within the brain can ensure that the drug reaches its target neurons.

Conclusion

10. No claim is allowed.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Hidalgo Pareja (WO 03/035033, published 1 May 2003, PCT filed 24 October 2002). The reference does not qualify as prior art, as foreign priority document Australia PS-2958 discloses the methods now claimed and antedates the filing date of Pareja. Note however

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Pareja's foreign priority document antedates applicant's foreign priority date. However, according to MPEP §706.02(f), foreign priority documents cannot be relied upon in determining if an application qualifies as prior art under 35 USC 102(e). Hidalgo Pareja teaches that MT cannot cross the BBB on its own, but that when placed inside a liposome is able to do so. Furthermore the reference teaches that MT in a liposome will be able to treat neurological conditions characterized by increased oxidative stress and cell death (see p. 4 for example).

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/

Primary Examiner, Art Unit 1649

February 13, 2009